

Milk iron content in breast-feeding mothers after administration of intravenous iron sucrose complex

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Abstract

Objective: To study the transfer of parenteral iron sucrose into maternal milk in the postpartum period.

Study design: Ten healthy lactating mothers with functional iron deficiency 2–3 days after delivery received 100 mg intravenous iron sucrose and were observed together with a control group (n=5) without iron treatment during four days. Milk samples were taken before the treatment and every day afterwards.

Results: Mean milk iron levels at baseline were 0.43 and 0.46 mg/kg in the treatment and control group and decreased until the end of observation in both groups by 0.11 mg/kg. No significant difference between the groups was found on any study day as well as in the mean change from baseline over all four days.

Conclusion: We could not show transfer of iron-sucrose into maternal milk for the given dosage. Since parenteral iron sucrose is widely used in obstetrics, the results provide information about safety of parenteral iron sucrose in the lactation period. The findings are also in agreement with other reports on active biological mammary gland regulation of milk iron concentration.

Keywords: Iron content; iron sucrose; lactation; milk; mother; postpartum.

Introduction

Postpartum iron deficiency, with or without anemia, is a frequent problem, which may be treated with intravenous

iron supplements. As this route of administration leads to temporary high serum iron levels, concern exists about the amount of iron that reaches the breast-fed infants. This is important, because iron overload could increase the risk of bacterial gastro-intestinal infection for the infant [4]. Intravenous iron sucrose complex is increasingly used in the peripartum period [1–3, 8, 11, 12], however, no definite correlation between serum iron levels and milk iron concentrations was observed, because the assumption is that milk iron content is rather independent from circulating iron [5]. However, clinical data on milk iron levels after intravenous iron administration are not available.

Hence, a study on iron transfer into the mother's milk was required or, equivalently, a proof of low iron content in breast milk after intravenous iron treatment. The study aimed to show no relevant increase in milk iron levels as compared to pretreatment values.

Because milk produced after delivery is known to show decreasing iron concentrations over time [13], the investigation considered a control group in a parallel group study design for clear interpretation of the measurements after iron administration. If elevated iron concentrations after intravenous supplementation were found, additional determination of lactoferrin bound iron in the milk was planned, since lactoferrin helps prevent iron overload in the infant by its iron binding capacity [4].

Patients and methods

The *study plan* included 15 lactating mothers with functional iron deficiency (transferrin saturation <15%) and mild anemia (hemoglobin 10–12 g/dL), but otherwise normal laboratory values, absence of infection and malignancy, and no history of intravenous iron supplementation within the last three weeks.

Sufficient milk and a healthy infant was a further prerequisite as well as written informed consent for study participation. In ten patients a single dose of 100 mg intravenous iron sucrose (iron(III)-hydroxide sucrose complex; trade name Venofer® (Vifor International Inc., St. Gallen, Switzerland) was administered on day 0 of the study. The other five patients served as controls and did not receive any iron preparation. Laboratory examinations were done on day 0 prior to iron administration and thereafter every day until day 4. Milk samples of 5–10 mL were collected directly after breast-feeding at between 08:00 and 18:00 h. The samples were frozen at –18° and sent for analysis for milk iron concentrations to an experienced laboratory using atomic absorption spectroscopy by ICP-OES instrument OPTIMA 3000 (Perkin Elmer Instruments, Norwalk, CT). The intended second step of determining the lactoferrin bound iron was

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Table 1 Patients' characteristics and hematology at study entry.

Parameter	Iron sucrose Mean (SD)	Control group Mean (SD)	Group comparison*
Age (years)	32.8 (6.0)	30.0 (4.4)	n.s.
Body weight (kg)	72.3 (4.4)	68.4 (7.1)	n.s.
Hemoglobin (g/dL)	11.0 (0.45)	11.7 (0.90)	n.s.
RBC count ($10^{12}/L$)	3.79 (0.37)	3.83 (0.50)	n.s.
Serum iron ($\mu\text{mol}/L$)	9.77 (4.7)	10.9 (4.9)	n.s.
Transferrin ($\mu\text{mol}/L$)	39.7 (8.1)	41.0 (12.0)	n.s.
Transferrin saturation (%)	11.9 (4.7)	12.9 (3.0)	n.s.

**t*-test; RBC and transferrin by Mann-Whitney *U*-test. n.s.; not significant ($P > 0.05$).

dropped, since total iron examinations showed low values during the follow-up days in all of the 15 subjects.

Statistical analysis

Mean values of the double readings of iron concentrations in milk were used. Due to some skewness of the data, group comparisons were done by Wilcoxon-Mann-Whitney test (Mann-Whitney *U*-test). Because the study investigated only the question of a possible increase of iron content in the treatment group, one-sided tests with more statistical power were performed. Other parameters were compared between study groups either by *t*-test or by Wilcoxon-Mann-Whitney test, as appropriate (two-sided). Significance threshold was defined by $\alpha = 0.05$ ($P \leq 0.05$). Primary parameter of the study consisted of the milk iron concentrations after day 0.

Results

Demographic data

Mean age of the mothers in the treatment and control group was 32.8 and 30.0 years. Measurements of body weight showed 72.3 and 68.4 kg on average (Table 1).

Hematological values

Mean hemoglobin values of 11.0 and 11.7 g/dL at study start indicated subnormal findings. Functional iron deficiency was documented by transferrin saturation of <15% (means of 11.9% and 12.9%, respectively) and was accompanied by serum iron of 9.8 and 10.9

$\mu\text{mol}/L$ on average. Group differences were not significant (Table 1).

Treatment and follow-up documentation

Of the 15 mothers included in the study on day 0, 10 were given the full dose of 100 mg intravenous iron sucrose. The 4-day observation period started in both study groups 2–3 day after the child was born, after secretion of colostrum had begun. No other iron preparations were taken at any time during the study.

Patients' adherence to the study protocol was given as complete milk samples collected from each of the 15 participants until the end of the regular study.

Milk iron concentrations

Milk iron content at baseline was similar in both study groups. Mean concentrations of 0.43 and 0.46 mg/kg found in the treatment and control group were not significantly different (Table 2). The 4-day observation period showed decreasing mean iron concentrations in both study groups (Figure 1). Only on the first post-treatment day some increase occurred in the control group due to a single elevated measurement. Mean decrease after four days reached about 0.11 mg/kg in both groups and mean change from baseline over all four days was again very similar in treated and untreated patients. Accordingly, no statistically significant intergroup difference was observed on any day or in regard to the averaged mean decrease of all four days (Table 2).

Table 2 Milk iron content (mg/kg) on start day 0 and change from baseline during follow-up.

Time course	Iron sucrose Mean (SD)	Control group Mean (SD)	Median difference ^Δ	Significance* P-value
Day 0 (baseline)	0.43 (0.10)	0.46 (0.11)	–	–**
Day 1 (change)	–0.07 (0.11)	+0.04 (0.22)	–0.04	0.84
Day 2 (change)	–0.10 (0.12)	–0.11 (0.13)	+0.01	0.43
Day 3 (change)	–0.11 (0.14)	–0.16 (0.19)	+0.05	0.34
Day 4 (change)	–0.11 (0.18)	–0.11 (0.12)	–0.04	0.67
Mean change, day 1–4	–0.096 (0.12)	–0.085 (0.11)	–0.026	0.66

*Mann-Whitney *U*-test (one-sided); **comparison at baseline: $P = 0.86$ (two-sided).

^Δneg./pos. sign means iron sucrose showed lower/higher values than control group.

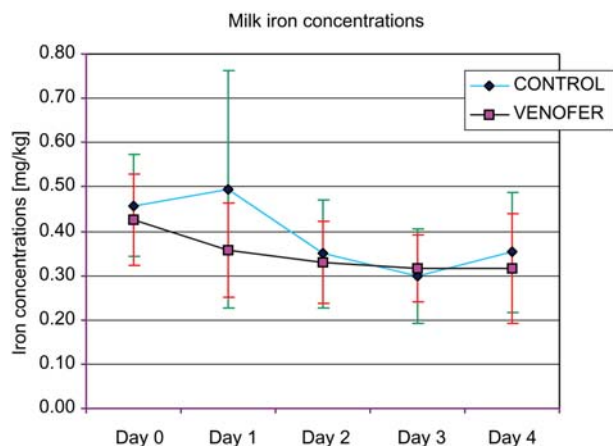


Figure 1 Milk iron content before and after administration of 100 mg intravenous iron on day 0 (mean \pm SD).

Due to the small samples of the study, power analysis was done in order to determine which minimal true group difference would result in statistical significance. Taking the SD values of the mean change parameter of all four days on Table 2, it resulted for the study groups with 10 and 5 patients with a power of 80% to detect a difference of 0.165 mg/kg at the 5% significance level ($P \leq 0.05$; one-sided *t*-test).

This means non-significance does not exclude a possible group difference of up to about 0.17 mg/kg but a larger difference is likely to be detected as statistically significant.

Discussion

Iron determinations in breast milk before and after a 100 mg IV dose of iron sucrose showed mean values of about 0.30–0.45 mg/kg, being in the lower range of known early postpartum milk iron levels. These levels were reported with numerous variations depending on the time after delivery, how milk samples were collected (sample volume and daytime), and possible population influences [6, 7, 9, 13]. At the beginning of the study, 2–3 days after delivery, treatment and control group were comparable in regard to functional iron deficiency parameters in blood and baseline milk iron levels, which decreased during the 4-day follow-up in a similar way in both groups by about 0.11 mg/kg. Corresponding to the follow-up with a similarity of the groups, no statistical significant differences were found on any of the four days or regarding the mean value of all four days.

Although the similar course of the two study groups may lead to the assumption of no group difference and hence no suspicion of possibly higher iron values in the treatment group, the study result may nevertheless have occurred by chance if the samples considered were too small. Therefore power analysis was performed, which

indicated that for the sample sizes chosen, the detectable difference was about 0.17 mg/kg. This means that the true population values might be higher than observed by that extent. However, these iron contents would again represent low findings, since they would still lie within the range of values reported from subjects without postpartum iron treatment or from non-anemic, healthy mothers [7, 9, 14, 15].

The result of decreasing milk iron levels after the 100 mg intravenous iron dose may be intriguing, however, postpartum milk iron content is known to decrease in healthy untreated subjects [13]. Another critique might relate to the first sample after the iron treatment taken only on the next day. A missed increase of milk iron content immediately after iron injection may indeed be a valid consideration. One must, however, also question if such short and transient elevation could be harmful for the infant when the subsequent feeding days contain normal values. We think rather not. In addition, the following fact supports the notion that milk iron content is probably not elevated during the first hours after an intravenous iron injection. No significant correlation between milk iron and iron status parameters of the mother, or intake of oral iron supplements, was found in various reports on postpartum milk iron contents [15]. Moreover, serum iron on day 0 before administration of iron sucrose was not significantly correlated with milk iron concentrations, although some dependency may not be excluded. Due to those observations, an active biological regulation of iron uptake by mammary glands is strongly supposed [10, 15], because it explains the laboratory findings in the milk. The results of our investigation also support this assumption.

In conclusion, in this study postpartum administration of 100 mg intravenous iron sucrose did not lead to enhanced iron contents of the colostrum during the following days but shows levels in the range of untreated healthy mothers. The findings are in agreement with other reports on postpartum subjects with or without oral iron supplementation leading to the assumption of a regulation of milk iron concentrations by active mammary gland mechanisms, by which breast-fed infants are protected from iron overload.

References

- [1] Bayoumeu F, C Subiran-Buisset, N Baka: Iron therapy in iron deficiency anemia in pregnancy: intravenous route versus oral iron route. *Am J Obstet Gynecol* 186 (2002) 518
- [2] Breymann C, R Richter, R Hüttnerx, R Huch, A Huch: Effectiveness of rhEPO and iron sucrose versus iron therapy only, in patients with postpartum anaemia and blunted erythropoiesis. *Eur J Clin Invest* 30 (2000) in press
- [3] Breymann C, E Visca, R Huch, A Huch: Efficacy and safety of intravenous iron sucrose with and without rhEPO for

- resistant iron deficiency anaemia in pregnancy. *Am J Obstet Gynecol* 184 (2000) 662
- [4] Bullen J, E Griffiths: Iron-binding proteins and host defence. *Iron and infection*. Second edition. John Wiley and Sons, London 1999 p 327
- [5] Domellof M, B Lonnerdal, K Dewey, R Cohen, O Hernell: Iron, zinc, and copper concentrations in breast milk are independent of maternal mineral status. *Am J Clin Nutr* 80 (2004) 111
- [6] Feeley R, R Eitenmiller, J Jones: Copper, iron, and zinc contents of human milk at early stages of lactation. *Am J Clin Nutr* 37 (1983) 443
- [7] Fransson G, B Lonnerdal: Iron in human milk. *J Paediatr* 96 (1980) 380
- [8] Hoigné R, C Breymann, U Künzi, F Brunner: Parenteral iron therapy: problems and possible solutions. *Schweiz Med Wochenschr* 128 (1998) 528
- [9] Lonnerdal B, C Keen, L Hurley: Iron, copper, zinc, and manganese in milk. *Ann Rev Nutr* 1 (1981) 149
- [10] Lönnerdal B: Regulation of mineral and trace elements in human milk: exogenous and endogenous factors. *Nutr Rev* 58 (2000) 223
- [11] Momem AA, AA Meshari, LA Nuaim, A Saddique, Z Abotalib, T Khashoggi, et al.: Intravenous iron sucrose complex in the treatment of iron deficiency anemia during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 69 (1996) 121
- [12] Perewusnyk G, R Huch, A Huch, A Krafft, C Breymann: Parenteral iron therapy in obstetrics: 8 years experience with iron sucrose complex. *Br J Nutr* 88 (2002) 3
- [13] Siimes M, E Vuori, P Kuitunen: Breast milk iron – a declining concentration during the course of lactation. *Acta Paediatr Scand* 68 (1979) 29
- [14] Silvestre D, C Martinez-Costa, M Lagarda, J Brines, R Farre, G Clemente: Copper, iron, and zinc contents in human milk during the first three months of lactation. *Biol Trace Element Res* 80 (2001) 1
- [15] Zavaleta N, J Nombera, R Rojas, L Hambraeus, J Gislason, B Lonnerdal: Iron and lactoferrin in milk of anaemic mothers given iron supplements. *Nutr Res* 15 (1995) 681

Received July 24, 2006. Revised November 1, 2006. Accepted December 7, 2006.